REMARKS

Claims 1-14 are pending. Claims 1, 3, 6, 7, and 11 have been amended. Support for the amendments can be found in the Specification as filed, for example, 8:30-31 and 9:26-27. The following addresses the substance of the Office Action and the Examiner Interview.

1. Title of the invention is not descriptive

The Examiner has requested amending the Title of the Invention to clearly indicate the invention to which the claims are directed. Applicant has now amended the Title accordingly.

2. References in IDS not found in File

Applicant has resubmitted the references previously submitted in the parent application in Applicant's co-pending Application No. 10/660,924 of which the present application is a continuation. Accordingly, pursuant to 37 C.F.R. 1.98(d), additional copies of the references are not submitted in the present application.

3. Compliance with 35 USC §112, second paragraph

The Examiner has rejected Claims 1-14 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. More specifically, the examiner has stated that there is insufficient antecedent basis for the limitation "curative" in the claim. During the interview on March 21, 2005, the Examiner indicated that the use of the term "therapeutic" would be acceptable. Applicant has now amended claims 1, 3, 6, 7, and 11 to recite the term "therapeutic" instead of "curative". Support for this amendment can be found on page 8, line 30-31 of the Specification as filed. Claim 6 was additionally rejected as being indefinite and ambiguous in the recitation of "wherein said tolerizing and curative doses are porcine", because "doses" can not be porcine. Applicant has amended claim 6 to read "wherein said tolerizing and therapeutic doses comprise porcine cells." Support for this amendment can be found in the Specification as filed, page 9, lines 26-27. Therefore, Claims 1-14 are now in compliance with 35 USC §112, second paragraph.

4. Compliance with 35 USC §112, first paragraph

The Examiner has rejected Claims 1-14 under 35 U.S.C. 112, first paragraph, as being not in compliance with the enablement requirement. The Examiner stated that the specification does not reasonably provide enablement for a method of treating Type I diabetes in a mammal

comprising implanting a tolerizing dose of insulin-producing cells encapsulated in a biologically compatible membrane and then administering a curative dose of corresponding unencapsulated insulin-secreting cells. According to MPEP 2164:

> "The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." A patent need not teach, and preferably omits, what is well known in the art."(2164.01)
>
> There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. "not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted. All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art."

Here, the scope of the claims is a method of inducing tolerance to insulin-producing cells implanted in an animal, including human, for the therapeutic result of treating diabetes. Every element of claim 1 is well within the level of knowledge of a skilled artisan, e.g., implanting foreign cells is common practice by medical doctors specializing in transplants; encapsulating methods are also well-known to a person skilled in the art, and Patent 5,529,914 which has been incorporated by reference into the Specification as filed teaches methods of encapsulating cells for implantation; calculating tolerizing dose and therapeutic dose for a specific mammal is disclosed in Examples 1 to 7 as "one or two orders of magnitude less than a curative dose". These examples give the tolerizing dose and therapeutic dose for several important medical conditions as follows:

Disease	Cells	Tolerizing Dose	Curative (Therapeutic) Dose	Support in the Specification
Diabetes	Islets/insulin producing cells	100-2,000 islets/kg of body weight 1,500 islets/kg of body weight	10,000-20,000 islets/kg of body weight 15,000 islets/kg of body weight	12:26-30 25:13-16
Parkinson's	Adrenal Chromaffin cells	1,000 cells/kg of body weight	10,000 cells/kg of body weight	25:21-26
Hemophilia	Liver cells	2,500 cells/kg of body weight	5,000 cells/kg of body weight	25:29-26:5

Disease	Cells	Tolerizing Dose	Curative (Therapeutic) Dose	Support in the Specification
Liver Transplant	Liver cells	1,000 cells/kg of body weight	Whole liver	26:7-11
Myasthenia gravis	Neural cells expressing acetylcholine receptor	2,500 cells/kg of body weight		26:13-19
General		Between about 100 cells/kg body weight and about 5,000 cells/kg body weight	Between about one and two orders of magnitude higher than tolerizing dose	13:1-4

Based on the guidance provided, a person skilled in the art would immediately know the dose required for their patient depending on the condition to be treated. Medical doctors routinely calculate dosages for patients by considering such factors, including but not limited to, weight, age, sex, degree of disease, etc. A curative (therapeutic) dose of implanted islets is well known in the field and a person skilled in the arts could readily calculate a one to two magnitude decrease in this dose to obtain the numbers for the tolerizing dose.

The specification also provides experimental proof of principle, i.e. experimental data showing that an encapsulated insulin-producing cells given as a small mass insufficient by itself to induce normoglycemia permits a second, unencapsulated, implant of insulin-producing cells in a therapeutic dose to survive as shown by normalized blood glucose levels in the treated mice in which diabetes had been induced by intravenous injection of streptozotocin. See Example 1.

Nevertheless, the Examiner is questioning the value of such evidence based on alleged lack of predictability of the treatment of diabetes in human from *in vivo* data obtained in murine models of diabetes. However, the Examiner is setting forth a much stricter standard than required by law. MPEP 2107.03 establishes the following:

> Evidence does not have to be in the form of data from an art-recognized animal model for the particular disease or disease condition to which the asserted utility relates. Data from any test that the applicant reasonably correlates to the asserted utility should be evaluated substantively. Thus, an applicant may provide data generated using a particular animal model with an appropriate explanation as to why that data supports the asserted utility. The absence of a certification that the test in question is an industry-accepted model is not dispositive of whether data from an animal model is in fact relevant to the asserted utility. Thus, if one skilled in the art would accept the animal tests as being reasonably predictive of utility in humans, evidence from those tests should be considered sufficient to

support the credibility of the asserted utility."

In the Declaration by David Scharp, M.D. submitted under 37 CFR §1,132, additional data is presented which shows that the claimed method works in two murine models of diabetes: the streptozotocin-induced diabetic mice and in non-obese diabetic (NOD) mice. These are the two well-known and widely accepted murine models of diabetes. The multiple low-dose streptozotocin (MLDS) model of diabetes is characterized by progressive hyperglycemia and insulitis similar to that observed in recent onset type I diabetics (Like and Rossini, 1976 *Science* **193**:415-417). The NOD mouse model also shares clinical serological and histo-immunological features with human type I diabetes (Bach, 1994 *Endocrine Rev.* **15**:516-542). As in humans, the disease is characterized by infiltration of the pancreatic islets by immune cells, insulitis followed by destruction of the β-cells. Both models have been used extensively to study new therapies for diabetes. In fact, the NIH recognize the NOD mouse as THE model animal for diabetes and maintains a research colony and data base on these animals for researchers. The NIH state "The NOD mouse, which spontaneously develops type 1 diabetes, is a valuable animal model that is used extensively in research exploring the etiology, prevention, and treatment of this disease. It is a vital research tool for testing promising prevention and treatment strategies at the preclinical level." (http://www.niaid.nih.gov/dait/NODmice.htm, copy attached herein).

The evidence in the Declaration reiterates the results provided in the specification showing that the claimed method is effective to permit survival of a therapeutic dose of insulin-producing cells and thereby effectively treating diabetes. *See* Declaration ¶ 6. Moreover, the Declaration also establishes that implantation of a sub-therapeutic, tolerizing dose of insulin-secreting cells is effective to create immunological tolerance to insulin-secreting cells, namely the host's own islet cells. Together these results establish that the claimed method of treating diabetes by tolerizing the host immune system prior to implanting the fully therapeutic dose of the insulin-producing cells works to permit the host to receive the fully therapeutic dose without rejection. *See* Declaration ¶¶ 7-16.

Therefore, using the proper standard set forth in the MPEP, the evidence provided by Applicant in the Specification and in the Declaration submitted herewith clearly supports that one skilled in the art would accept the murine models as reasonably correlating to the condition in human.

The Examiner also believed that undue experimentation would be required to determine screening and testing protocols. However, as is apparent from the claim, the goal of the invention is to treat diabetes, i.e. achieve and maintain normoglycemia. Methods for determining whether normoglycemia is present have been exceedingly well known for many years; only routine blood glucose monitoring would be required to demonstrate the efficacy of the claimed invention.

5. Compliance with 35 U.S.C. 103(a)

The Examiner has rejected Claims 1-4 and 6-14 under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,703,017 or by US Patent 5,425,764, or US Patent 5,629,194 each in view Posselt et al. (1991 *Ann. Surg.* **214**:363-373). Pursuant to MPEP 2143, in order to establish a *prima facie* case of obviousness three requirements must be met: First there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. In the case of the present invention, the cited references fail to suggest all of the claim limitations.

The '017 patent describes implanting insulin-producing cells in a dose of about 8,000-12,000 islets/kg of patient's body weight (col. 14, lines 7-9) to create a pancreas-like structure in a human patient. Therefore, the implant in USP '017 is designed to treat diabetes by creating a live "insulin pump" in the body. Furthermore, Example 12 of USP '017 describes implanting 5,000 islets per NOD mouse (this dose equals 200,000 islet/kg of body weight), which resulted in normoglycemia in these animals. The '017 patent does not teach or suggest implanting a dose of insulin-producing cells encapsulated in a biologically-compatible membrane prior to implanting the fully-therapeutic dose, wherein the tolerizing dose is at least one order of magnitude less than the therapeutic dose.

US Patent 5,425,764 describes a method of using an implantable bioartificial pancreas device containing insulin-secreting islets, to supply an exogenous source of insulin to treat the symptoms of diabetes. Accordingly, the '764 patent requires implantation of a therapeutic dose of insulin-secreting cells, i.e. the dose necessary to achieve normoglycemia. As such, the '764 Patent does not describe or suggest implanting a tolerizing dose of insulin-producing cells

encapsulated in a biologically-compatible membrane prior to implanting of fully therapeutic non-encapsulated dose, where the tolerizing dose is at least one order of magnitude less than the therapeutic dose.

US Patent 5,629,194 describes a method of implanting embryonic porcine pancreatic non-insulin-secreting cells capable of proliferating *in vivo* and then secreting insulin after transplantation. The dose sufficient for the treatment of insufficient insulin activity is 100,000-500,000 aggregates, each containing 300-500 cells per human patient. This is a fully therapeutic dose. Thus, the '194 patent does not describe or suggest implanting a tolerizing dose of insulin-producing cells encapsulated in a biologically-compatible membrane prior to implanting of fully therapeutic non-encapsulated dose, where the tolerizing dose is at least one order of magnitude less than the therapeutic dose.

Posselt et al. describes implanting unencapsulated islets into various areas of the body, liver, kidney, and thymus, of spontaneously diabetic BB rats. The only implantation site that showed survival of the implanted cells was the thymus. The intrathymic islet recipients were observed for a period close to the life span of the rat, without any recurrent diabetes. In additional experiments, approximately 100 days after the initial intrathymus transplantation, the transplanted rats were challenged with an extrathymic allogeneic islets, which remained intact even after removal of the thymus bearing the islet allografts. However, as the authors stated several times in this article, thymus is considered to be an immunologically privileged site and is subject to the usual biologic characteristics of such sites, in that prior sensitization of the host with skin allografts precludes prolonged survival of intrathymic islets (page 272, right column). The experiments, performed by Posselt et al. show just that, i.e. when allogeneic islets were transplanted into the thymus of recipients that had previously rejected donor strain skin grafts, the islets were destroyed in an accelerated manner, demonstrating that the intrathymic site is readily accessible to activated T cells (page 367 left column, and page 368, right column), and that no tolerance can be achieved using this protocol. Furthermore, Posselt et al. goes on stating that the achieved tolerization to intrathymic allografts is due to their direct influence on maturing thymocytes, which are more susceptible to tolerance-inducing signals, and that such "inappropriate" presentation of antigen by nonlymphoid cells induce a state of anergy in T cells (page 373). Therefore, Posselt et al. teaches away from using tolerizing dose of insulin-producing cells anywhere but thymus, and it does not teach encapsulating these cells.

Furthermore, as Dr. Scharp states in his Declaration submitted herewith, the BB rat has multitude of immunologic disorders that makes it more of a model for immune deficiency than for diabetes. Therefore, the BB rat is no longer considered an acceptable model for studying human autoimmune diabetes. This is also stated by Posselt et al.: "BB rats are known to be significantly immunodeficient" (see page 365, left column, line 5-6).

Here, the instant method is not limited to any specific implantation site for the tolerizing dose of encapsulated cells and still ensures survival of subsequently implanted un-encapsulated cells. Furthermore, opposite to Posselt et al., it works even in models where the immune system has already been sensitized.

Therefore, none of the cited references suggest the claimed limitation that a tolerizing dose is implanted prior to a therapeutic dose. Accordingly, even when combined, these references do not teach all the limitations of the claimed invention. As such, the cited references fail to support a *prima facie* case of obviousness. Therefore, Claims 1-4 and 6-14 are in compliance with 35 U.S.C. 103.

The Examiner has rejected Claim 5 under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,703,017 or by US Patent 5,425,764, or US Patent 5,629,194 each in view Posselt et al. (1991 *Ann. Surg.* **214**:363-373) as applied to Claims 1-4 and 6-14, and further in view of USP 5,529,914. Non-obviousness of the independent Claim 1 in view of US Patent 6,703,017 or by US Patent 5,425,764, or US Patent 5,629,194 each in view Posselt et al. is asserted above. The US Patent 5,529,914 discloses a method of encapsulating cells, but it fails to cure the deficiencies of US Patent 6,703,017, US Patent 5,425,764, US Patent 5,629,194, and Posselt et al. Therefore, Claim 5 is in compliance with 35 USC §103(a).

CONCLUSION

Applicants have endeavored to address all of the Examiner's concerns as expressed in the outstanding Office Action. Accordingly, amendments to the claims, the reasons therefor, and arguments in support of the patentability of the pending claim set are presented above. In light of the above amendments and remarks, reconsideration and withdrawal of the outstanding rejections is specifically requested. If the Examiner finds any remaining impediment to the prompt allowance of these claims that could be clarified with a telephone conference, the Examiner is respectfully requested to initiate the same with the undersigned.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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By: Daniel Altman

Daniel Altman
Registration No. 34,115
Attorney of Record
Customer No. 20,995
(949) 760-0404

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050605